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Clinical Analysis of a Large Kindred With the Pallister Ulnar-Mammary Syndrome

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The ulnar-mammary syndrome (UMS) is an autosomal dominant disorder characterized by posterior limb deficiencies or duplications, apocrine/mammary gland hypoplasia and/or dysfunction, abnormal dentition, delayed puberty in males, and genital anomalies. We present the clinical descriptions of 33 members of a six generation kindred with UMS. The number of affected individuals in this family is more than the sum of all previously reported cases of UMS. The clinical expression of UMS is highly variable. While most patients have limb deficiencies, the range of abnormalities extends from hypoplasia of the terminal phalanx of the 5th digit to complete absence of the ulna and 3rd, 4th, and 5th digits. Moreover, affected individuals may have posterior digital duplications with or without contralateral limb deficiencies. Apocrine gland abnormalities range from diminished axillary perspiration with normal breast development and lactation, to complete absence of the breasts and no axillary perspiration. Dental abnormalities include misplaced or absent teeth. Affected males consistently undergo delayed puberty, and both sexes have diminished to absent axillary hair. Imperforate hymen were seen in some affected women. A gene for UMS was mapped to chromosome area 12q23-q24.1. A mutation in the gene causing UMS can interfere with limb patterning in the proximal/distal, anterior/posterior, and dorsal/ventral axes. This mutation disturbs development of the posterior elements of forearm, wrist, and hand while growth and development of the anterior elements remain normal. © 1996 Wiley-Liss, Inc.

KEY WORDS: ulnar-mammary syndrome, Pallister ulnar-mammary syndrome, Schinzel syndrome, limb development, posterior limb deficiency, polydactyly, apocrine gland hypoplasia, autosomal dominant inheritance, delayed puberty, absent axillary hair

INTRODUCTION

Upper limb deficiencies occur in 3–4 of every 10,000 live births [Froster and Baird, 1992; Czeizel, 1994] and are classified according to the anatomic location of the abnormality (preaxial, involving the anterior or radial side of the limb, or postaxial, involving the posterior or ulnar side of the limb). The prevalence of isolated ulnar deficiencies is 1–2/100,000 [Källén et al., 1984], although ulnar deficiencies are often elements of more common disorders (e.g., Brachmann-deLange syndrome).

The ulnar-mammary syndrome (UMS; OMIM 181450) is an autosomal dominant disorder characterized by posterior limb deficiencies or duplications, apocrine/mammary gland hypoplasia and/or dysfunction, abnormal dentition, delayed puberty in males, and genital anomalies. It was originally described by Gilly [1882] in a woman with mammary hypoplasia, inability to lactate, and absence of the 3rd to 5th digits and ulna. Over the last century approximately 24 affected individuals in 8 families were described [Franceschini et al., 1992; Gonzales et al., 1976; Hecht and Scott, 1984; Meinecke et al., 1989; Pallister et al., 1976; Schinzel et al., 1987; Sherman et al., 1986]; we are aware of at least two additional, unreported families.

We describe the clinical findings of the UMS in a kindred with 33 affected relatives in six generations (Fig. 1). Twenty-three of these individuals were ascertained in Utah and participated in a project which mapped a gene for UMS to chromosome area 12q23-12q24.1 [Bamshad et al., 1995]. Subsequently, a common ancestor between the Utah family and the kindred reported by Pallister et al. [1976] was identified. That is the individual labeled I-3 in Figure 1 (the pedigree) of Pallister et al. [1976] who is labeled II-3 in our pedigree (Fig. 1). Consequently, the clinical findings of the affected in-

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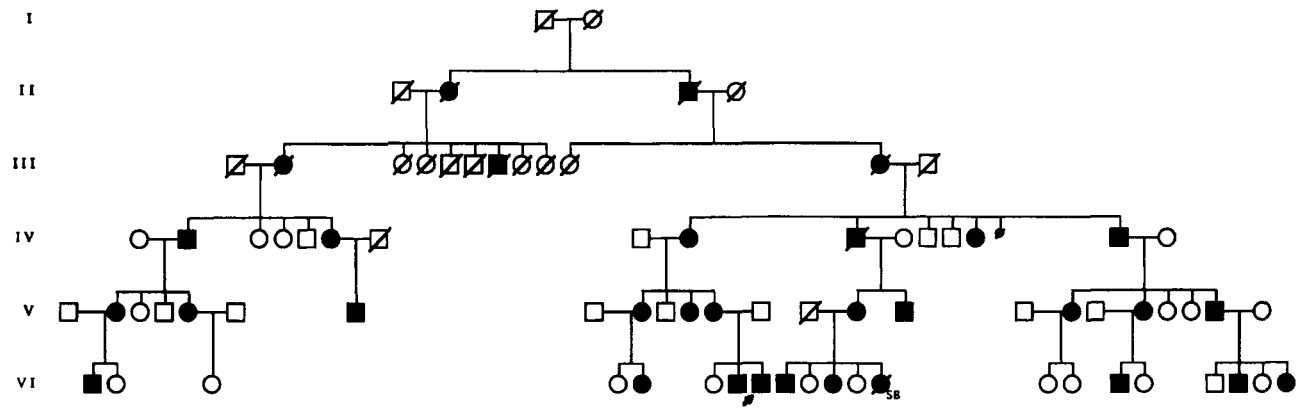


Fig. 1. Abbreviated pedigree of Family L. Individuals are referred to as if numbered from left to right beginning with number one. Darkened circles (females) and squares (males) indicate affected individuals. Unrelated spouses and unaffected relatives are illustrated by white icons. The individual labeled I-3 in Figure 1 (the pedigree) of Pallister et al. [1976] is labeled II-3 in our pedigree.

dividuals in the UMS pedigree of Pallister et al. [1976] were included and extended in this report.

CLINICAL REPORTS

The propositus (VI-8) is a male who was delivered at 38 weeks estimated gestational age to a 28 year-old gravida 3, para 2, Caucasian mother. Prenatal ultrasonography had been performed, and the fetus was reported as normal. Pregnancy, labor, and delivery were uncomplicated. Birthweight was 4,090 g (90th centile), and length was 53.3 cm. (75th–90th centile). He had bilateral upper limb anomalies. Neonatal course and subsequent growth and development were normal. He was referred for evaluation of limb malformations.

At 2 months his weight was 5,100 g (50th centile), length was 58.7 cm (50th centile), and the head circumference (OFC) was 41 cm (95th centile). Skull was normal, and forehead, midface, and chin, palpebral fissures, intercanthal distance, and eye findings were normal. He had a capillary hemangioma in the middle of his forehead, on the right side of his nasal tip and philtrum, and on his posterior neck. Neck was normal; he had mild pectus excavatum. Cardiac, abdominal, and genital findings were normal. His neurologic status was unremarkable.

Both upper limbs were abnormal. The right 3rd, 4th, and 5th metacarpals and digits and ulna were absent (Fig. 2). His right radius was bowed, and his forearm short. The proximal and distal flexion creases of his 1st and 2nd digits were hypoplastic. The 5th digit of his left hand could not be flexed, and the proximal and distal flexion creases of his 4th and 5th digits were hypoplastic. His lower limbs were normal. Roentgenograms confirmed clinical findings.

AFFECTED RELATIVES

All studies were performed with the approval of the Institutional Review Board of the University of Utah and the General Counsel of the Shriner's Hospitals for Crippled Children. After obtaining informed consent all living relatives were evaluated by interview and physical examination. Roentgenograms were obtained on selected individuals; 21 affected relatives were examined, and their findings are listed in Table I. Two additional individuals, a stillborn child (VI-13) and a spontaneously miscarried fetus (IV-15), were labeled as affected based on their physical descriptions by relatives. Individuals in the family reported by Pallister et al. [1976] were interviewed, and this information is included Table I. One additional affected individual (VI-1) has been added to the Pallister et al. [1976] pedigree, and this family has been related to the Utah kindred by way of the common ancestors I-1 and -2 in Figure 1.

Limb malformations ranged from partial duplication of the nail on the ventral surface of the 5th digit (Figs. 3 and 4) to absence of 4th and 5th digits accompanied

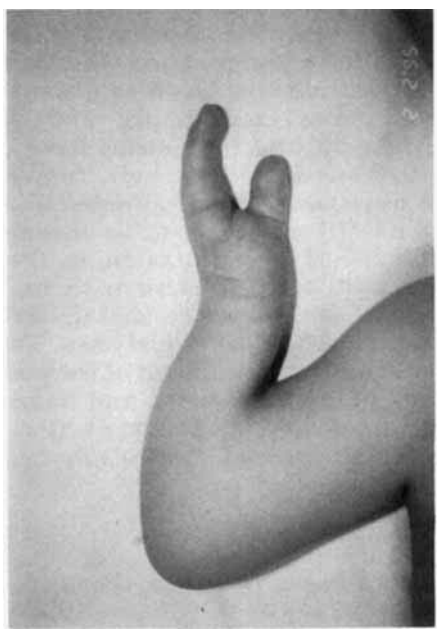
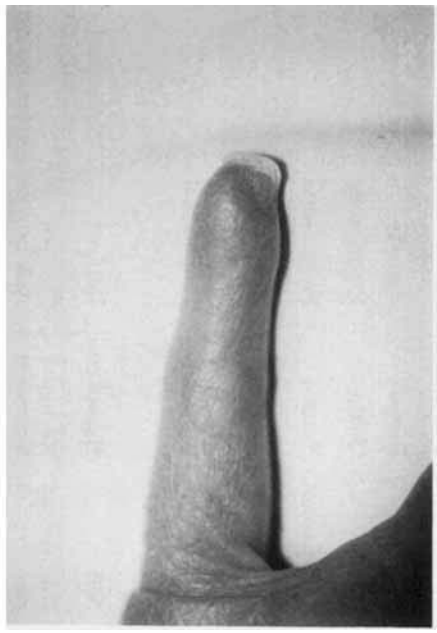


Fig. 2. Propositus at age 10 months. Note absence of the ulna and metacarpals and phalanges of digits 3, 4, and 5. The radius is bowed and the forearm is short.



Figs. 3 and 4. Ventral duplication of the nail of the 5th digit. Additionally the digit is tapered, and the interphalangeal creases are absent.

by ulnar and radial hypoplasia (see Fig. 3 in Pallister et al. [1976]). Some individuals presented with polydactyly and contralateral posterior upper limb deficiency. Not all affected individuals had limb deficiencies; some had bilateral posterior polydactyly. Individuals with duplication malformations produced offspring with limb deficiencies and vice versa. Not all affected individuals had abnormalities of the limbs that could be detected clinically or radiographically.

Apocrine abnormalities ranged from a supernumerary nipple to hypopigmentation and bilateral hypoplasia of the areola, nipple, and breast. All affected individuals had diminished or absent axillary hair. Apocrine dysfunction ranged from diminished axillary perspiration to absence of axillary perspiration. Lactation ranged from normal to absent. An imperforate hymen was reported by three women. All affected males experienced a delayed onset of puberty. Ectopic or absent canine teeth were reported in three individuals. No association was observed between the severity of the limb deficiency and apocrine or endocrine abnormalities. No evidence of anticipation or a parent-of-origin effect was identified in this kindred.

DISCUSSION

We have studied the manifestations of 33 affected individuals in six generations of a family with UMS. Our clinical analysis suggests that hypoplasia and partial or complete fusion of the phalanges of the 5th digit is the most common limb abnormality identified in affected individuals. This is consistent with the findings of Franceschini et al. [1992] who summarized 22 of the previously reported cases and found a short/stiff 5th digit in 59.1% of affected individuals. Although "decreased sweating" and "absent/sparse axillary hair" were reported by Franceschini et al. [1992] in 63.6% and 50.0% of affected individuals, respectively, each postpubertal affected individual in the family we studied had these manifestations.

We have expanded the range of phenotypic expression of UMS to include mammary duplications by documenting the co-segregation of accessory nipples in three affected individuals. Likewise, partial ventral duplication of the nail of the 5th digit was observed in five affected individuals. Although wide phenotypic variation has been documented within and among previously reported UMS families, it is unknown whether the same gene much less the same mutation is responsible for UMS in each family. Heterogeneity does not explain the phenotypic variability of UMS in this single large kindred suggesting that epistatic mechanisms are responsible, in part, for the observed morphological and functional variation observed between individuals.

To perform linkage analysis we developed a set of strict diagnostic criteria for UMS. An individual was diagnosed as affected based on a family history of a posterior limb duplication and/or deficiency and the presence of two or more of the following diagnostic criteria: hypoplastic or absent elements of the posterior limb, posterior polydactyly, duplication of the nail of the 5th digit, mammary hypoplasia, supernumerary nipples, diminished axillary sweating and a lack of body odor, sparse or absent axillary hair, a decreased ability to lactate in females, and delayed puberty in males. Haplotype analysis suggests that the presence of two or more of these criteria discriminated between affected and unaffected individuals [Bamshad et al., 1995]. Abnor-

TABLE I. Manifestation of Ulnar Mammary Syndrome in the Present Family*

	Limb				Apocrine				Endocrine	Other
Pedigree number	Posterior polydactyly	Posterior deficiency	Digital fusion	Nail abnormality	Axillary hair	Perspiration	Lactation	Breasts	Puberty	
VI-1 M	R		L 5th phalanges				N/A	Unknown	Prepubertal	
VI-5 F				Ventral duplication			Nulliparous	Normal	Prepubertal	
VI-7 M		R ulna; R 3, 4, 5th metacarpals and phalanges						Normal	Prepubertal	
VI-8 M			R/L 5th middle and distal phalanges				N/A	Normal	Prepubertal	
VI-9 M	R				Absent	Absent	N/A	Hypoplastic	Delayed	Diminished axillary folds
VI-11 F	R/L				Absent	Absent	Nulliparous	Normal	Delayed	
VI-13 F			"Stiff" 5th digit					Unknown	N/A	Spontaneously aborted fetus
VI-16 M			R/L 5th phangles				N/A	Normal	Prepubertal	
VI-19 M		"Tapered" 5th digit					N/A	Hypoplastic	Delayed	Ectopic canines
VI-21 F		R/L 5th distal phalanges					Nulliparous	Unknown	Prepubertal	
V-2 F		"Not visibly affected"			Absent	Absent	Unknown	Hypoplastic	Normal	
V-5[a] F	R	L ulna; L 4, 5th metacarpals and phalanges; R short 5th metacarpal			Reduced	Absent	Unknown	Hypoplastic	Normal	Imperforate hymen; absent canines;
V-7 M			L 5th phalanges		Absent	Absent	N/A	Unknown	Delayed	Obese
V-9 F	R/L				Reduced	Diminished	Normal	Normal	Normal	Cleft palate
V-11 F	R/L				Absent	Absent	Nulliparous	Normal	Normal	Imperforate hymen
V-12 F		L 5th distal phalanx			Reduced	Diminished	Normal	Normal	Normal	

(continued)

TABLE I. (*continued*)

	Limb				Apocrine				Endocrine	Other
Pedigree number	Posterior polydactyly	Posterior deficiency	Digital fusion	Nail abnormality	Axillary hair	Perspiration	Lactation	Breasts	Puberty	
V-15 F		L 5th distal phalanx			Absent	Absent	Absent	Normal	Normal	
V-16 M			R/L 5th phalanges	Ventral duplication	Reduced	Diminished	N/A	Unknown	Delayed	
V-18 F	R/L				Absent	Diminished	Diminished	Normal	Normal	
V-20 F	R/L				Absent	Diminished	Normal	Normal	Normal	
V-23 M		R/L 5th distal phalanx			Reduced	Absent	N/A	Hypoplastic	Delayed	Ectopic canines
IV-2 M	R	L 5th phalanges			Absent	Absent	N/A	Unknown	Delayed	
IV-6 F			R/L 5th phalanges		Absent	Absent	Unknown	Hypoplastic	Normal	Imperforate hymen
IV-9 F				Ventral duplication	Absent	Absent	Absent	Normal	Normal	
IV-10 M			R/L 5th phalanges		Unknown	Unknown	N/A	Unknown	Delayed	Deceased
IV-14 F		L ulna; L 5th metacarpals and phalanges	R 5th proximal/ middle phalanges		Absent	Absent	Nulliparous	Hypoplastic	Delayed	
IV-15 F			R/L 5th phalanges		N/A	N/A	N/A	Unknown	N/A	Stillborn
IV-16 M				Ventral duplication	Absent	Absent	N/A	Supernumerary nipples	Delayed	
III-2 F					Absent	Absent	Absent	Unknown	Normal	Deceased
III-7 M			R/L 5th phalanges		Unknown	Unknown	N/A	Unknown	Delayed	Deceased
III-11 F			R/L	Ventral duplication	Unknown	Unknown	Unknown	Unknown	Normal	Decreased
II-2 F			"Stiff and crooked" 5th digits		Unknown	Unknown	Unknown	Unknown	Normal	Deceased
II-3 M	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	N/A	Unknown	Delayed	Deceased

* R, right; L, left; N/A, not applicable.
[a] Index case of Pallister et al. [1976].

malities of axillary hair and apocrine gland function were consistent in all affected post-pubertal individuals, and all affected males older than 16 years exhibited delayed pubertal development, while not all affected individuals had clinically recognizable limb abnormalities. Thus, in the absence of a family history of a posterior limb duplication and/or deficiency, the presence of three diagnostic criteria in females and four in males is required to substantiate the diagnosis of UMS .

Schinzel [1987] suggested that the inability to breast-feed "probably caused grossly reduced numbers of surviving offspring to affected mothers in earlier centuries." This conclusion is tempered by the findings that in this family, lactation is variably reduced in affected females, ranging from absence of lactation (no postpartum engorgement was noted either) to normal lactation. Additionally, Schinzel [1987] speculated that male fertility was reduced, and this seemed to "correlate" with the extent of the posterior limb deficiency. If fertility is estimated by the number of offspring produced, then neither of these findings are supported by our analysis since affected males produced a mean of 3.4 children (excluding unmarried males).

It has been speculated that UMS is allelic to hand-foot-uterus syndrome (HFUS; OMIM 140000) [Rogers and Anderson, 1995]. HFUS is an autosomal dominant disorder that was originally described by Stern et al. [1970]. Manifestations of HFUS which are similar to these of UMS include digital hypoplasia, carpal fusion, supernumerary nipples, and genital anomalies. A causal relationship between split-hand/split-foot (SHSF) syndrome and UMS has also been suggested [Lenz, 1980], and an individual with UMS and absence of only the 4th digit has been reported [Franceschini et al., 1992]. The scalp-ear-nipple syndrome (SENS; OMIM 181270) also overlaps the UMS on the basis of mammary hypoplasia, diminished axillary perspiration, and dental abnormalities [Edwards et al., 1994]. However digital syndactyly is the characteristic limb anomaly found in individuals with SENS, not limb deficiencies or duplications. The two individuals reported by Sherman et al. [1986] had mammary hypoplasia, diminished axillary perspiration, abnormally shaped ears, and digital syndactyly of the lower limbs. Additionally, the 23-year-old affected woman suffered from hypertension (J. Sherman, personal communication). Therefore, we suggest that these individuals may have SENS, not UMS.

A gene causing UMS has recently been mapped to a 21 cM region, bracketed by recombinants in affected individuals, on the distal end of the long arm of chromosome 12 between markers D12S78 and D12S86. This corresponds to the physical region between 12q23 and 12q24.1 [Bamshad et al., 1995]. A more recent linkage analysis incorporating additional relatives has improved the lod score to 7.65 at $q = 0.00$ with the marker D12S79 (M. Bamshad, unpublished data). This region contains a locus for Holt-Oram syndrome (HOS; OMIM 142900) suggesting that the genes for UMS and HOS may be allelic or closely linked [Basson et al., 1994; Bonnet et al., 1994; Terret et al., 1994]. The pleiotropic anomalies of UMS have been compared to HOS [Pallister et al., 1976], yet posterior limb abnormalities are uncommon in HOS, and isolated anterior limb abnormalities have not been reported in UMS. SHSF disorders are heterogeneous, but to our knowledge no gene for SHSF has been mapped to 12q23-q24.1. Furthermore, it is now possible to test whether HFUS and/or SENS are allelic with UMS or caused by mutations in a gene closely linked to the UMS gene.

Since the sequence and spatial arrangements of bony elements of the limb are consistent among vertebrates, it has been argued that there exists a unique developmental strategy for building limbs [Duboule, 1994]. This strategy is mediated by a network of signaling factors that regulate limb outgrowth and patterning in the proximal/distal, anterior/posterior, and dorsal/ventral axes [Martin, 1995]. Shubin and Alberch proposed that the branching and segmentation pattern of limb outgrowth follows the humerus and ulna, skewing anteriorly to produce the digital arch [Shubin and Alberch, 1986; Oster et al., 1988]. Yet a mutation in the gene causing UMS is apparently capable of disrupting the posterior elements of the forearm, wrist, and hand while growth and development of the anterior elements remain normal. Furthermore, the UMS gene may also be involved in dorsal/ventral patterning, as a duplicated fingernail can be produced on the distal ventral fingertip in affected individuals. Thus, a mutation in the UMS gene interferes with patterning and growth of all three limb axes.

The UMS gene product must also be involved in the development and growth of apocrine/mammary glands, the process of lactation, and the regulation of the onset of male puberty. Genes modulating epithelial-mesodermal interactions are known to be involved in limb and apocrine development. Cloning and characterization of the UMS gene and analysis of disease mutations will be an important step toward understanding the molecular basis of such interactions.

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